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10/560,956	07/24/2006	Peter Lockyer	MKC-008	1674

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/560,956	LOCKYER, PETER	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-80* is/are pending in the application.

4a) Of the above claim(s) *64,67 and 78-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-63,65,66 and 68-77* is/are rejected.

7)☒ Claim(s) *60-63,65,66 and 68-77* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 December 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0706*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Invention I(A)(I)(M) in their response of May 13, 2008 is acknowledged. The elected invention is directed to a low through-put method for identifying a compound capable of promoting deactivation or inhibiting activation of membrane bound wild-type H-Ras GTPase.

Applicants' traversal is based on the following arguments.

(A) Mochizuki et al, 2001 fails to teach or describe special technical features shared by independent claims 60 and 77, and claims depending therefrom. In contrast to Mochizuki et al, Applicant's invention does not relate to a FRET-based assay. Rather, it involves translocation of a reporter from the cytosol to associate with or dissociate from a small membrane bound GTPase of interest. The reporter has a detectable marker and a small GTPase binding moiety, the latter being an effector of the small GTPase or derived therefrom (e.g. a Raf 1 RBD or derivative thereof).

(B) Mochizuki fails to teach or suggest monitoring the association of a reporter with a membrane bound small GTPase or a membrane bound active Ras, as required by Applicants' claims. First, Mochizuki et al does not monitor a membrane bound active Ras, as required by the claims. Rather, a chimeric protein consisting of H-Ras, RBD, YFP, and CFP is used. Second, Mochizuki fails to teach or suggest monitoring the association of a reporter with a membrane bound active Ras or that dissociation of the reporter from the membrane bound active Ras indicates that a test compound is capable of promoting deactivation of the active Ras. Third, Mochizuki's assay only measures intrinsic activity of their chimera. It does not measure actual activity of endogenous Ras. Conversely, Applicant's' claimed invention can measure the actual

activity of various endogenous small GTPases inside a cell, for example, a tumor cell expressing oncogenic Ras or hyperactive normal Ras.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: As explained in the prior action, the technical feature linking Groups I(A)-(N) appears to be that they all relate to cellular, reporter methods for identifying an inhibitor of a GTPase and Mochizuki et al teach a cellular, reporter method for identifying an inhibitor of a H-Ras GTPase (pg 1067, parg 3), which anticipates Claim 1. It is acknowledged that Mochizuki's method is FRET-based; however the instant claims encompass FRET-based assays (specification; [0094]). The claims fail to recite the limitation of translocation of a reporter from the cytosol to associate with or dissociate from a small membrane bound GTPase. The reporter of Mochizuki has a detectable marker and the binding moiety Raf1 RBD (Fig 1; pg 1065, parg 3).

(B) Reply: Mochizuki's assay monitors the association of the intramolecular reporter, Raf 1 RBD-CFP, with a membrane bound H-RAS as a means to detect activity of the H-RAS (Fig 1 & 2; pg 1066, parg 5). The claims encompass use of a protein comprising H-RAS. Mochizuki et al teaches that dissociation of the Raf 1 RBD-CFP reporter from the membrane-bound active Ras indicates that a test compound, AG1478, is capable of promoting deactivation of the active Ras (Fig 1; pg 1067, parg 3). It is noted that the instant claims do not recite the GTPase and binding motif/reporter as separate molecules. It is acknowledged that Mochizuki's assay only measures activity of their chimera; however, the instant claims are not limited to measurement for the activity of an endogenous GTPase. It is noted that Mochizuki et al does

teach use of variants of H-Ras, including hyper-active variants, in their assay (pg 1066, parg 3; pg 10).

For these reasons and those explained in the prior action, the restriction requirement is still deemed proper and is therefore made FINAL.

Claims 60-80 are pending. Claims 64, 67, and 78-80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 60-63, 65, 66, and 68-77 are hereby examined.

Priority

The priority date granted for the instant invention is June 26, 2003, the filing date of UK 03149804, which disclosed the elected invention.

Drawings-Objections

Figure 2, filed July 24, 2006, is objected to for comprising three sequences but having five sequence identifier numbers (SEQ ID NOs:). Clarification is required.

Figure 5 is objected to because neither the figure nor the legend thereto explain what transcript is being analyzed.

Abstract-Objections

The abstract is objected to because it is a single, run-on sentence.

MPEP 608.01(b) states

> The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claims-Objections

Claims 60-63, 65, 66, and 68-77 are objected to for encompassing non-elected subject matter.

Claim 60, line 3, is objected to for "incubating in the presence of a test compound a live cell expressing…", which would be better stated as "incubating, in the presence of a test compound, a live cell expressing…".

For Claim 61, line 4, the phrase "secretory vesicles" should be corrected to "secretory vesicle membranes".

For Claim 69, line 3, the phrase "the small GTPase relative to…" should be corrected to "the small GTPase, relative to…".

For Claim 75, line 4, "imaging and confocal imaging" should be corrected to "imaging, and confocal imaging".

For Claim 76, line 2, "tumor cell and a cell from an in vitro model…" should be corrected to "tumor cell, and a cell from an in vitro model…".

Claim 77, line 3, is objected to for "incubating in the presence of a test compound a live cell expressing…", which would be better stated as "incubating, in the presence of a test compound, a live cell expressing…".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 60-63, 65, 66, and 68-77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claims 60 and 77 are indefinite because they fail to recite what result is indicative that the test compound is capable of inhibiting activation. Claims 61-63, 65, 66, and 68-76, as dependent from Claim 60, are indefinite for the same reason.

Claim 61 is indefinite for an improper Markush group; on line 4, "and" should be corrected to "or".

Claim 66 is indefinite because it fails to be encompassed by the claim from which it depends, Claim 60. Claim 66 recites a method using one or more GTPases; however, Claim 60 recites a method using only a single GTPase. The skilled artisan would not know the metes and bounds of the recited invention.

For Claim 69, the phrase "peptide derived from an effector of the small GTPase having one or more point mutations" renders the claim indefinite. It is unclear whether said phrase means that the peptide has mutations or that the GTPase has mutations. The skilled artisan would not know the metes and bounds of the recited invention. For purposes of examination, it is assumed that "peptide derived from an effector of the small GTPase having one or more point mutations" means that the peptide has mutations. If this assumption is correct, it is suggested that "peptide derived from an effector of the small GTPase having one or more point mutations" be amended to "peptide, derived from an effector of the small GTPase, having one or more point mutations".

For Claims 71 and 77, the term "derivative" renders the claims indefinite. Neither the claims nor the specification define the metes and bounds of the derivatives encompassed by said claims. For purposes of examination, it is assumed that the encompassed derivatives have any function of the parent molecule and any structure.

Claim 75 is indefinite and confusing for a possible improper Markush group. It is unclear whether "and" on line 4 is meant to be "and"; in which case, all of the listed methods would be used. Alternatively, is "and" on line 4 is meant to be "or"? In which case, only one of the listed methods would be used.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 60-63, 65, 66, and 68-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method, using COS cells, for identifying a compound capable of promoting deactivation or inhibiting activation of membrane bound wild-type H-Ras GTPase using a reporter comprising Raf-1 RBD linked to EGFP, does not reasonably provide enablement for a method for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase in any cell using any reporter construct and any detection method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In regards to this enablement rejection, the application disclosure and claims are compared per the factors indicated in the decision In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but are not limited to: (1) the nature of the invention; (2) the breath of the claims; (3) the predictability or unpredictability of the art; (4) the amount of direction or guidance presented; (5) the presence or absence of working examples; (6) the quantity of experimentation necessary; (7) the relative skill of those skilled in the art. Each factor is here addressed on the basis of a comparison of the disclosure, the claims, and the state of the prior art in the assessment of undue experimentation.

Claims 60, 61, 72, and 76, are so broad as to encompass any method for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase in essentially any cell using any reporter construct and any detection method. Claims 62, 63, 65, 66, and 68-76 are dependent from Claim 60 and add the following limitations: (62, 63) Ras superfamily GTPase, (65, 66) a Ras GTPase, (68-70) the reporter construct comprises a GTPase-specific binding moiety, (71) Raf-1 RBD, (73) luminescent or fluorescent protein, and (74, 75) fluorescence microscopy. Claim 77 is so broad as to encompass any method for identifying a compound capable of promoting deactivation of any Ras GTPase in any cell using a GFP-RBD reporter construct, or any derivative thereof, and any detection method. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods broadly encompassed by the claim.

The specific reagents and steps used for any methods determines the method's success. Predictability of which steps and reagents can be used to obtain the effect requires a knowledge of, and guidance with regard to how said steps and reagents relate to the desired outcome; in this case, identifying cellular modulators of any GTPase. Predictability of which of the large number of possible reporters can be used in any cell for assessing the activity of any GTPase requires a knowledge of, and guidance with regard to which moieties bind to any GTPase in an activity-dependent manner, which detectable markers can be used in which cell types and can be analyzed using which detection systems, and which cells can be successfully used for the recited method. However, in this case the disclosure is limited to a method, using COS cells, for identifying a compound capable of promoting deactivation or inhibiting activation of membrane bound wild-type H-Ras GTPase using a reporter comprising Raf-1 RBD linked to EGFP.

While recombinant and mutagenesis techniques and methods for detecting numerous markers are known, it is not routine in the art to make an unlimited number of reporters, comprising any GTPase binding moiety and any marker, and then test said unlimited number of reporters, in an unlimited number of cell types, for activity-dependent binding to any GTPase using any detection system. Furthermore, the ways in which any GTPase binding moiety, any marker, cell type, or detection system may or may not be altered with a reasonable expectation of success of retaining the desired analysis/utility are limited in any method and the results of such modifications are unpredictable (Kalhammer et al, 1997). In addition, one skilled in the art would expect any tolerance to modification for a given method to diminish with each further and additional modification.

The specification does not support the broad scope of Claims 60-63, 65, 66, and 68-76, which encompasses all methods for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase in essentially any cell using any reporter construct and any detection technique or said method having the additional limitation of (62, 63) Ras superfamily GTPase, (65, 66) a Ras GTPase, (68-70) the reporter construct comprises a GTPase-specific binding moiety, (71) Raf-1 RBD, (73) luminescent or fluorescent protein, and (74, 75) fluorescence microscopy. The specification does not support the broad scope of Claim 77, which encompasses all methods for identifying a compound capable of promoting deactivation of any Ras GTPase in any cell using a GFP-RBD reporter construct, or any derivative thereof, and any detection method. The specification does not support the broad scope of Claims 60-63, 65, 66, and 68-77 because the specification does not establish: (A) all GTPase that can be successfully analyzed with the recited method; (B) all GTPase-specific binding moieties that can be successfully used in the recited method; (C) all detectable markers that can be successfully used in the recited method; (D) all reporters that can be successfully used in the recited method; (E) all cells that can be successfully analyzed with the recited method; (F) all detection technologies that can be successfully used in the recited method; (G) all combinations of GTPase, GTPase-specific binding moieties, detectable markers, reporters, cells, and detection technologies that can be successfully used in the recited method; and (H) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of methods with an enormous number of possible

steps and reagents used. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written Description

Claims 60-63, 65, 66, and 68-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 60-63, 65, 66, and 68-77 are directed to a genus of methods for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase in essentially any cell using any reporter construct and/or any detection technique. The specification teaches only a one representative species of such methods. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 69 is directed to a genus of methods for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase in any cell using a reporter construct comprising a binding moiety derived from a GTPase effector, wherein the binding moiety has point mutation(s) that increase the affinity for the GTPase. The specification teaches no representative species of such methods. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a method for identifying a compound capable of promoting deactivation or inhibiting activation of any GTPase. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 60-63, 65, 66, 68, and 70-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Mochizuki et al, 2001. Mochizuki et al teaches a microscopic, cellular (COS) method for assessing the activity of H-Ras using a reporter comprising Raf-1-RBD linked to the fluorescent protein CFP, wherein the reporter binds to H-Ras when active (Fig 1). Mochizuki et al further teaches using said method for identifying a compound capable of promoting deactivation or inhibiting activation of Ras (pg 1067; parg 3) and that the Ras is localized to the plasma membrane (Fig 2a; pg 1066, parg 5). Therefore, Claims 60-63, 65, 66, 68, and 70-77 are rejected under 35 U.S.C. 102(b) as being anticipated by Mochizuki et al, 2001.

Allowable Subject Matter

No claims are allowable.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages. It is also requested that the serial number of the application and date of amendment be referenced on every page of the response.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-092834. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
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